

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS**

ASTELLAS INSTITUTE FOR
REGENERATIVE MEDICINE **and** STEM
CELL & REGENERATIVE MEDICINE
INTERNATIONAL, INC.,

Plaintiffs,

v.

IMSTEM BIOTECHNOLOGY, INC.,
XIAOFANG WANG, **and** REN-HE XU,

Defendants.

Civil Action No. 1:17-cv-12239-ADB

[REDACTED]
[REDACTED]

**Leave to File Under Seal Granted on July
29, 2019 (Dkt. No. 74)**

**PLAINTIFFS' OPPOSITION TO DEFENDANTS' MOTION FOR LEAVE TO FILE
AMENDED COUNTERCLAIMS**

Table of Contents

I.	INTRODUCTION	1
II.	STATEMENT OF RELEVANT FACTS	3
	A. Astellas Possessed Both Its Innovative Method And Resulting Cells Prior To The First Communications With Defendants	3
	B. [REDACTED]	3
	C. Astellas’s Inventions Claimed In Its ’321 and ’956 Patents Stem From The Same Astellas Research Project	5
III.	ARGUMENT	5
	A. Defendants’ Proposed New Counterclaims Are Unduly Delayed, Made In Bad Faith And With Dilatory Motive.....	6
	1. Defendants’ Deliberate, Bad Faith Delay in Bringing Their Claims Concerning the ’321 Patent Warrants Denying Their Motion.....	6
	2. Defendants Fail to Establish Good Cause to add Dr. Xu to the Existing Counterclaim Concerning the ’956 Patent.....	9
	B. Defendants’ Proposed New Counterclaims Are Futile	10
	1. Comparing HB-MSD to BM-MSDs and Characterizing the Levels of IL-6 Made by HB-MSD are not Grounds for Inventorship	11
	2. Mitotic Inactivation is not Grounds for Inventorship	13
	3. Defendants’ Counterclaims Do Not Promote Judicial Economy	14
	C. Defendants’ Proposed Counterclaims Prejudice Plaintiffs	15
	D. Defendants’ Surreptitious Attempt to Add a New Affirmative Defense Should Be Denied.....	18
	1. Defendants Make no Attempt to Argue There is Good Cause to Add Their New Affirmative Defense.....	18
	2. Defendants’ New Affirmative Defense is Futile and Unduly Prejudicial.....	19
IV.	CONCLUSION.....	20

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Abbott Labs. v. Baxter Pharm. Prod., Inc.</i> , 471 F.3d 1363 (Fed. Cir. 2006).....	12
<i>AbbVie, Inc. v. Kennedy Trust for Rheumatology Research</i> , No. 13-cv-1358(PAC), 2014 WL 3360722 (S.D.N.Y. July 9, 2014)	15
<i>ACA Fin. Guar. Corp. v. Advest, Inc.</i> , 512 F.3d 46 (1st Cir. 2008).....	8
<i>Acromed Corp. v. Sofamor Danek Grp., Inc.</i> , 253 F.3d 1371 (Fed. Cir. 2001).....	11
<i>Astellas Inst. for Regenerative Med. v. ImStem Biotech., Inc.</i> , No. 1:17-cv-12239-ADB, 2018 WL 4685565 (Sept. 28, 2018)	10
<i>Calderón–Serra v. Wilmington Trust Co.</i> , 715 F.3d 14 (1st Cir. 2013).....	8
<i>In re Cumberland Farms, Inc.</i> , 284 F.3d 216 (1st Cir. 2002).....	19
<i>DiVenuti v. Reardon</i> , 37 Mass. App. Ct. 73 (1994).....	10, 18
<i>EMC Corp. v. Pure Storage, Inc.</i> , 310 F.R.D. 194 (D. Mass. 2015).....	16
<i>EMI Grp. N. Am., Inc. v. Cypress Semiconductor Corp.</i> , 268 F.3d 1342 (Fed. Cir. 2001).....	12
<i>Euro-Pro Operating LLC v. Dyson Inc.</i> , 164 F. Supp. 3d 235 (D. Mass. 2016)	17
<i>House of Clean, Inc. v. St. Paul Fire & Marine Ins. Co.</i> , 775 F. Supp. 2d 296 (D. Mass. 2011)	5
<i>Israel Bio-Eng’g Project v. Amgen, Inc.</i> , 475 F.3d 1256 (Fed. Cir. 2007).....	13
<i>Jakobsen v. Mass. Port Auth.</i> , 520 F.2d 810 (1st Cir. 1975).....	19

<i>Kader v. Sarepta Therapeutics, Inc.</i> , No. 1:14-cv-14318-ADB, 2017 WL 72396 (D. Mass. Jan. 6, 2017), <i>aff'd</i> 887 F.3d 48 (1st Cir. 2018).....	5
<i>Kay v. N.H. Democratic Party</i> , 821 F.2d 31 (1st Cir. 1987) (per curiam)	9
<i>Keystone Shipping Co. v. New England Power Co.</i> , 109 F.3d 46 (1st Cir. 1997).....	14
<i>Knapp Shoes, Inc. v. Sylvania Shoe Mfg. Corp.</i> , 15 F.3d 1222 (1st Cir. 1994).....	19
<i>Meng v. Chu</i> , 643 Fed. App'x 990 (Fed. Cir. 2016).....	13
<i>Mulder v. Kohl's Dep't Stores, Inc.</i> , 865 F.3d 17 (1st Cir. 2013).....	7, 10
<i>Nikitine v. Wilmington Tr. Co.</i> , 715 F.3d 388 (1st Cir. 2013).....	7, 9, 18
<i>Nikitine v. Wilmington Tr. Co.</i> , No. 11-1231(JAG), 2012 WL 12896162 (D.P.R. May 14, 2012), <i>aff'd</i> , 715 F.3d 388 (1st Cir. 2013).....	7
<i>O'Connell v. Hyatt Hotels of Puerto Rico</i> , 357 F.3d 152 (1st Cir. 2004).....	9
<i>Ohio Willow Wood Co. v. Alps S., LLC</i> , 735 F.3d 1333 (Fed. Cir. 2013).....	14
<i>Perlmutter v. Shatzer</i> , 102 F.R.D. 245 (D. Mass. 1984).....	19
<i>Redondo-Borges v. United States Dep't of Housing & Urban Dev.</i> , 421 F.3d 1 (1st Cir. 2005).....	18
<i>Steir v. Girl Scouts of the USA</i> , 383 F.3d 7 (1st Cir. 2004).....	5, 9
<i>Trans-Spec Truck Srvs., Inc. v. Caterpillar Inc.</i> , 524 F.3d 315 (1st Cir. 2008).....	6
<i>Villanueva v. United States</i> , 662 F.3d 124 (1st Cir. 2011).....	9

Other Authorities

Fed. R. Civ. 16(b)	5
Federal Rule of Civil Procedure 8(c)	19

I. INTRODUCTION

Defendants’ motion could give the impression that this is a friendly academic dispute about how to share credit for an invention. Not so. The scientists at Astellas Institute for Regenerative Medicine and Stem Cell & Regenerative Medicine International, Inc. (collectively “Astellas”) provided Drs. Wang and Xu and their company ImStem Biotechnology, Inc. (collectively “Defendants”) with confidential proprietary methods, powerful stem cells (“mesenchymal stem cells” or “MSCs”) generated by those methods, and training and advice on replicating their discoveries. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED].

When called to account for their behavior, Defendants doubled down on their misconduct. Dr. Wang styled himself an “inventor” for his role in conducting routine tests that merely confirmed what the Astellas scientists expected—that Astellas’s new methods resulted in superior MSCs.

Now, nearly two years into this litigation, Defendants are seeking to grab even more of Astellas’s technology. Using “case development” as an excuse, they now claim Drs. Wang and Xu are inventors of Astellas’s foundational and novel method for making MSCs and the resulting cells themselves, and that Dr. Xu contributed to Astellas’s methods of using its MSCs. These claims are patently and demonstrably baseless. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Defendants’ attempt to add new claims is nothing more than a last-ditch effort to salvage their case, after their original claims were wrecked in discovery. Their counsel’s invocation of “murky” principals of inventorship cannot change the simple and controlling fact that Defendants obtained MSCs and methods for making them from Astellas. Consequently, Defendants did not “invent” any inherent property of those cells, including their increased potency compared to cells generated by other methods or their decreased secretion of a chemical called “IL-6” compared to cells made by prior methods. Nor did they invent a well-known step for processing stem cells to address a known safety concern. For these reasons, Defendants’ motion is untimely, brought in bad faith with dilatory motives, prejudicial, and futile, and should be denied.

Furthermore, though not mentioned anywhere in their brief, Defendants’ clandestine effort to add an affirmative defense of statute of limitations should be denied. Defendants were fully aware when they answered the complaint of the time that had elapsed since launching their plot against Astellas, and they apparently concluded (correctly) that any applicable statute of limitations had been tolled by Defendants’ concealment and affirmative assurances to Astellas. This explains why Defendants offer no excuse for their delay, or even bother to mention it in their pleadings, apparently hoping it would slip by unnoticed. While late amendments are sometimes allowed in the interest of justice, justice should not reward Defendants for their complete failure to argue the basis for their amendment, or indeed to so much as mention it in their motion and accompanying memorandum.

II. STATEMENT OF RELEVANT FACTS

A. Astellas Possessed Both Its Innovative Method And Resulting Cells Prior To The First Communications With Defendants

There is no dispute that Astellas had possession of its innovative method for making hemangioblast-derived mesenchymal stem cells (“HB-MSCs”) and the resulting inventive HB-MSCs prior to its first communications with Defendants. There is also no dispute that Astellas provided Defendants with the confidential protocol for making HB-MSCs and the resulting HB-MSCs at the outset of their collaboration. (See D.I. 1 at ¶ 35; D.I. 20 at Ans. ¶ 35 (Defs. ImStem & Wang); D.I. 33 at Ans. ¶ 35 (Def. Xu); [REDACTED])

B. [REDACTED]

Early in the collaboration, Defendants repeatedly acknowledged that they would keep Astellas’s proprietary methods, cells, and data confidential. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Dr. Wang filed the first provisional application for ImStem’s patent that is the subject of Plaintiffs’ correction of inventorship claims (*i.e.*, U.S. Patent No. 9,745,551 (“the ’551 Patent”)).¹ (*See* D.I. 1-1 at “Related U.S. Application Data.”)

¹ As Defendants now admit, Drs. Kimbrel and Lanza should be added as at least co-inventors on the ’551 Patent. (*See* D.I. 71 at 3 n.6.) Defendants’ memorandum is the first instance that Astellas is aware of in which Defendants concede that both Drs. Kimbrel and Lanza should be co-inventors, or that Defendants have offered to make both of them co-inventors on the ’551 Patent. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

C. Astellas's Inventions Claimed In Its '321 and '956 Patents Stem From The Same Astellas Research Project

Astellas's U.S. Patent No. 8,961,956 ("the '956 Patent"), which is the subject of Defendants ImStem's and Wang's original counterclaim, is a continuation-in-part of Astellas's U.S. Patent No. 8,962,321 ("the '321 Patent"), which is the subject of Defendants' proposed new counterclaims. As expected of related patents, the subject matter described the '321 and '956 Patents is the result of the same research project—Astellas's development of a new method of making MSCs, the novel MSCs made from that method, and various uses of those novel MSCs. In general, the '321 Patent claims Astellas's methods of making MSCs from human embryonic stem cells through a hemangioblast intermediate ("HB-MSCs") and the resulting cells themselves. The '956 Patent claims methods of treating various diseases or disorders using Astellas's HB-MSCs, made by Astellas's innovative methods.

III. ARGUMENT

Where, as here, a motion to amend was filed after the deadline for amendment set forth in the scheduling order, "the more demanding 'good cause' standard of Fed. R. Civ. 16(b)" applies and "focuses on the diligence (or lack thereof) of the moving party." *Steir v. Girl Scouts of the USA*, 383 F.3d 7, 12 (1st Cir. 2004). "To show good cause, a party ***must demonstrate*** 'the deadline in the scheduling order may not reasonably be met, despite the diligence of the [moving] party.'" *House of Clean, Inc. v. St. Paul Fire & Marine Ins. Co.*, 775 F. Supp. 2d 296, 298 (D. Mass. 2011) (emphasis added) (citation omitted). Motions to amend may be denied, *inter alia*, for reasons of undue delay, the movant's bad faith or dilatory motive, undue prejudice to the opposing party, and futility of the amendment. *Kader v. Sarepta Therapeutics, Inc.*, No. 1:14-cv-14318-ADB, 2017 WL 72396, at *3 (D. Mass. Jan. 6, 2017), *aff'd* 887 F.3d 48 (1st Cir. 2018).

Here, Defendants fail to establish good cause to add either their proposed amended counterclaims or their covert new affirmative defense. The new counterclaims and defense spring from Defendants' bad faith and dilatory motive and are unduly delayed, futile, and prejudicial.

A. Defendants' Proposed New Counterclaims Are Unduly Delayed, Made In Bad Faith And With Dilatory Motive

Defendants know they did not invent the methods of producing HB-MSCs claimed in the '321 Patent. Their unduly delayed motion is yet another bad faith, dilatory tactic in an attempt to appropriate Astellas's invention and distract from the mounting evidence of Defendants' misappropriation and misuse of the confidential protocols and materials Astellas shared under the guise of collaboration. Such tactics should not be rewarded.

1. Defendants' Deliberate, Bad Faith Delay in Bringing Their Claims Concerning the '321 Patent Warrants Denying Their Motion

At the time of its Answer, Defendants were not "poorly positioned to determine the precise scope of their counterclaims." (D.I. 71 at 7.) To the contrary, they were in the best position of anyone to know what they invented and what they did not. Their proposed counterclaims are entirely "based on information that [they] had or should have had from the outset of the case." *Trans-Spec Truck Srvcs., Inc. v. Caterpillar Inc.*, 524 F.3d 315, 327 (1st Cir. 2008) (affirming denial of motion to amend for undue delay). Indeed, Defendants were aware of the '321 Patent when they filed their original counterclaims, as it is cited throughout that pleading. (*See, e.g.*, D.I. 20 at ¶¶ 27, 47, 51; and pages 19-20, Prayer for Relief at C.)

Not only did Defendants have plenty of time and necessary information to analyze the '321 Patent to identify whether or not Drs. Wang or Xu contributed anything to the claimed methods, Defendants actually did so. [REDACTED]

[REDACTED]

[REDACTED]

██████████ Within months of the filing of the complaint and well before the Court-ordered deadline for amending the pleadings, Defendants knew they had no basis to claim inventorship of methods they had nothing to do with.

Indeed, Defendants have known about the precise scope of what they could have counterclaimed because ██████████

██████████

██████████

██████████ Defendants continue this scheme now by “scrambling to devise new theories of liability based on the same facts [originally] pled,” *Mulder v. Kohl’s Dep’t Stores, Inc.*, 865 F.3d 17, 20 (1st Cir. 2013), in an attempt to further harm Astellas by suggesting there is a cloud over its ownership to its own inventions.

By Defendants’ own admissions, they had the necessary facts to decide whether they could raise any claims regarding the ’321 Patent at the time Defendants ImStem and Wang filed their counterclaims over a year and a half ago. Defendants admit that “with respect to the ’321 patent, the underlying facts are *essentially the same*” as those underlying the counterclaims pled in January 2018, and that the newly alleged counterclaims arise from the same collaboration. (D.I. 71 at 8-9) (emphasis added). Defendants also admit that Dr. Xu’s “claim to inventorship is identical to Dr. Wang’s.” (D.I. 71 at 10.) As such, Defendants’ new claims “could and should have been put forward in a more timeous fashion.” *Nikitine v. Wilmington Tr. Co.*, 715 F.3d 388, 391 (1st Cir. 2013) (“Importantly, ‘this is not a case of new allegations coming to light following discovery, or of previously unearthed evidence surfacing.’”) (citation omitted); *Nikitine v. Wilmington Tr. Co.*, No. 11-1231(JAG), 2012 WL 12896162, at *2 (D.P.R. May 14, 2012), *aff’d*, 715 F.3d 388 (1st Cir. 2013) (denying motion to amend for undue delay and dilatory motives,

because a party “should not be kept on the hook while counsel adjusts the [pleading] for previous failings, thereby gaining additional and unwarranted swings at the mound”).

Defendants’ delay of over a year and a half after filing their original answer and counterclaims to bring these new accusations should not be rewarded. Defendants cannot simply sit back, withhold information, hinder Astellas from collecting relevant discovery on the issues only Defendants knew may be relevant to this dispute, and then spring new theories and claims at the close of fact discovery. “It is black-letter law that ‘[r]egardless of the context, the longer a plaintiff delays, the more likely [a] motion to amend will be denied, as protracted delay, with its attendant burdens on the opponent and the court, is itself a sufficient reason for the court to withhold permission to amend.’” *ACA Fin. Guar. Corp. v. Advest, Inc.*, 512 F.3d 46, 57 (1st Cir. 2008) (citation omitted) (denying motion to amend where party “deliberately wait[ed] in the wings for a year and a half” after having the needed information); *see also Calderón–Serra v. Wilmington Trust Co.*, 715 F.3d 14, 20 (1st Cir. 2013) (“Appreciable delay alone, in the absence of good reason for it, is enough to justify denying a motion for leave to amend.”).

Even assuming that Defendants did not have the necessary facts to determine their own inventorship (they did) and that they were “poorly positioned” to assert their new inventorship claims prior to the amendment deadline (they were not), Defendants concede that they received all the information they needed to set forth their new counterclaims *at least four months ago*. (D.I. 71 at 7.) But Defendants did not notify Astellas of even the potential that they might seek to amend their claims at that time. Instead, Defendants left Astellas to pursue the current claims—preparing for and taking depositions of Drs. Wang and Xu—unaware of the possible relevancy of the new factual issues related to IL-6, relative potency of the HB-MSCs, or mitotic inactivation of the HB-MSCs. Further, during Defendants’ purposeful delay, the Court-ordered deadline for fact

discovery has passed. Defendants' deliberate decision to delay in bringing their new allegations justifies denying their motion. *See Villanueva v. United States*, 662 F.3d 124, 127 (1st Cir. 2011) (affirming finding of undue delay when four months had elapsed); *Kay v. N.H. Democratic Party*, 821 F.2d 31, 34–35 (1st Cir. 1987) (per curiam) (affirming finding of undue delay when three months had elapsed); *Steir v. Girl Scouts of the USA*, 383 F.3d 7, 12 (1st Cir. 2004) (affirming finding of undue delay when three months had elapsed and discovery had closed).

2. Defendants Fail to Establish Good Cause to add Dr. Xu to the Existing Counterclaim Concerning the '956 Patent

Astellas agrees with Defendants that, as the First Circuit has explained, “[e]verything depends on context” when deciding a motion to amend. (*See* D.I. 71 at 6 (citing *Nikitine v. Wilmington Tr. Co.*, 715 F.3d 388, 390 (1st Cir. 2013).) In *Nikitine*, the Court found a nine-month delay was undue where the party “offer[ed] absolutely no explanation” for the need for amendment. *Id.* The same relevant aspects here warrant the same result.

Defendants waited more than *nineteen* months after their original pleading was filed, and offered no explanation for their substantial delay in asserting that Dr. Xu should be co-inventor on the '956 patent, other than that he “lives in Macau and was difficult to communicate with before he came to the United States” for his deposition. (D.I. 71 at 7-8.) [REDACTED]

[REDACTED] [REDACTED] Regardless, Defendants' dubious references to communication difficulties do not establish the required good cause to amend the pleadings. *See O'Connell v. Hyatt Hotels of Puerto Rico*, 357 F.3d 152, 155 (1st Cir. 2004) (failure of communications between counsel across countries does not constitute “good cause”). Defendants also admit that Dr. Xu's “claim to inventorship is identical to Dr. Wang's,” (D.I. 71 at 10), based on facts long in Defendants' possession. Indeed, the new factual averments about Dr. Xu with respect to the '956 patent reference an alleged meeting *with Dr. Wang*. (D.I. 71-

2 at Counterclaim ¶ 17.) These failures to even attempt to provide explanations for their delay further evidence Defendants’ gamesmanship to “devise new theories of liability based on the same facts [originally] pled.” *Mulder v. Kohl’s Dep’t Stores, Inc.*, 865 F.3d 17, 20 (1st Cir. 2013); *DiVenuti v. Reardon*, 37 Mass. App. Ct. 73, 77 (1994) (“Among the good reasons, however, for which a motion to amend may be denied are that no justification for the lateness of the motion is apparent (beyond counsel for the moving party having had a late dawning idea) . . .”).

B. Defendants’ Proposed New Counterclaims Are Futile

Defendants’ motion to amend should be denied for the independent reason that the proposed claims are futile—whether brought as counterclaims or in a separate action. A joint inventor is required to “(1) contribute *in some significant manner* to the conception or reduction to practice of the invention, (2) make a contribution to the claimed invention *that is not insignificant in quality*, when that contribution is measured against the dimension of the full invention, and (3) *do more than merely explain to the real inventors well-known concepts* and/or the current state of the art.” *Astellas Inst. for Regenerative Med. v. ImStem Biotech., Inc.*, No. 1:17-cv-12239-ADB, 2018 WL 4685565 at *3 (Sept. 28, 2018) (quoting *Israel Bio-Eng’g Project v. Amgen, Inc.*, 475 F.3d 1256, 1264 (Fed. Cir. 2007)) (emphasis added). Defendants’ proposed new claims cannot meet this standard.

It is undisputed that Defendants did not contribute to the novel method of deriving HB-MSCs, the inventive core of the ’321 Patent. [REDACTED] Instead, Defendants allege three bases on which they purport to have contributed to certain claims of the ’321 Patent: (1) the relative potency of Astellas’s HB-MSCs compared to bone marrow derived MSCs (“BM-MSC”); (2) characterizing the amount of a chemical called IL-6 secreted by Astellas’s HB-MSCs; and (3) mitotically inactivating Astellas’s HB-MSCs. (See D.I. 71 at 5.) None of these contribute to

Astellas's inventive method and cells or do anything more than explain well-known concepts or the current state of the art.

1. Comparing HB-MSC to BM-MSCs and Characterizing the Levels of IL-6 Made by HB-MSC Are Not Grounds for Inventorship

Even assuming that Defendants' new allegations in their proposed amended counterclaims regarding IL-6 and the relative potency of HB-MSCs and BM-MSCs are true, such activities did not contribute to the conception or reduction to practice of Drs. Kimbrel and Lanza's invention. Moreover, if anything, such activities would be "insignificant in quality" when measured against the scope of Drs. Kimbrel and Lanza's invention of the HB-MSCs themselves. *Acromed Corp. v. Sofamor Danek Grp., Inc.*, 253 F.3d 1371, 1379 (Fed. Cir. 2001) ("Beyond conception, a purported inventor must show that he made 'a contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention.'") (citation omitted).

Defendants' proposed amended counterclaims allege that during the collaboration they "chemically 'characteriz[ed]' the cells (*e.g.* as to the anti-inflammatory cytokine IL-6) and compar[ed] them to bone-marrow-derived MSCs." (D.I. 71-2 at Counterclaim ¶ 26.) They also allege that the "idea of [] comparing HB-MSCs to bone-marrow-derived MSCs and determining greater potency is a valuable aspect of the invention that gave rise to the '321 Patent [and] Drs. Wang and Xu contributed this idea." (*Id.* at ¶ 43.) Notably, Defendants do not allege any facts supporting their assertion that either this characterization or this idea are valuable or inventive.

But even assuming these conclusory allegations are true (which they are not), these concepts are neither significant, nor actual inventive concepts. The novelty of the claims comes from Astellas's novel method to generate a new type of MSC, derived through a particular type of intermediate cell, not for observing the properties of those new cells. It is a "general principle that

a newly-discovered property of the prior art cannot support a patent on that same art.” *Abbott Labs. v. Baxter Pharm. Prod., Inc.*, 471 F.3d 1363, 1368 (Fed. Cir. 2006). This is akin to the Federal Circuit’s guidance that “[h]umans lit fires for thousands of years before realizing that oxygen is necessary to create and maintain a flame[; t]he first person to discover the necessity of oxygen certainly could not have obtained a valid patent claim for ‘a method of making a fire by lighting a flame in the presence of oxygen.’” *EMI Grp. N. Am., Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1351 (Fed. Cir. 2001).

Defendants made no modifications to the claimed methods and cells in the ’321 Patent that impact whether Astellas’s HB-MSCs are more potent than BM-MSCs or their levels of IL-6. Rather, at best, Defendants merely gathered data points on the innate characteristics of Astellas’s inventive cells. Worse, even accepting Defendants’ allegations as true, Defendants did no more than apply concepts that were known in the art. For example, scientists already knew to compare the properties of MSCs derived from different cell sources. (*See, e.g.*, Ex. 8 (Jong Ha Hwang et al., *Comparison of Cytokine Expression in Mesenchymal Stem Cells from Human Placenta, Cord Blood, and Bone Marrow*, 24 J. KOREAN MED. SCI. 547 (2009)).) The act of comparing Astellas’s new HB-MSCs to known MSCs from other sources is not a significant or inventive concept. Similarly, it was well known that MSCs (derived from various sources) secreted IL-6 and that IL-6 has a role in autoimmune diseases, such as multiple sclerosis. (*See, e.g.*, Ex. 9 (Chae Woon Park et al., *Cytokine Secretion Profiling of Human Mesenchymal Stem Cells by Antibody Array*, 2 INT. J. STEM CELLS 59 (2009)); Ex. 10 (Ruo-Pan Huang et al., *The Promise of Cytokine Antibody Arrays in the Drug Discovery Process*, 9 EXP. OP. THERAPEUTIC TARGETS 601 (2005)).) As such, measuring the IL-6 levels secreted by Astellas’s novel HB-MSCs was nothing more than routine, and the amount of secretion is merely a property of the cells the Astellas scientists made. There

simply is no “invention” in routinely quantifying the intrinsic IL-6 secretion levels of these MSC cells. *See Meng v. Chu*, 643 Fed. App’x 990, 996 (Fed. Cir. 2016) (finding party not entitled to be added as joint inventor because efforts were not “anything beyond that of ordinary skill in the profession” and actions requiring “nothing more than the use of ordinary skill in the art . . . would not normally be a sufficient contribution to amount to an act of joint inventorship”).

2. Mitotic Inactivation is Not Grounds for Inventorship

Next, Defendants claim “Drs. Wang and Xu also conceived of the idea of mitotically inactivating the HB-MSCs (*e.g.* by irradiation) so that the cells, when used clinically, would be unable to divide/reproduce/differentiate into unwanted cell types (*e.g.* cancer tumors), while still retaining their therapeutic effect.” (D.I. 71-2 at Counterclaim ¶ 27.) But this was a well-known safety step, whereby any stem cells (including MSCs) should be mitotically inactivated before putting them in a living animal to prevent the cells from dividing uncontrollably (*i.e.* becoming cancer). (*See, e.g.*, Ex. 11 (Betül Çelebi et al., *Irradiated mesenchymal stem cells improve the ex vivo expansion of hematopoietic progenitors by partly mimicking the bone marrow endosteal environment*, 370 J. IMMUNOLOGICAL METHODS 93 (2011) (AIRM00297371); Ex. 12 Bocelli-Tyndall, Chiara, et al. *Bone marrow mesenchymal stromal cells (BM-MSCs) from healthy donors and auto-immune disease patients reduce the proliferation of autologous-and allogeneic-stimulated lymphocytes in vitro*, *Rheumatology* 46.3 (2007): 403-408.) The prior art describes numerous ways to inactivate MSCs, such as chemically or by irradiation.

Even if Drs. Wang and Xu had first thought of the idea of mitotically inactivating HB-MSCs (which they did not), this would not make them joint inventors because this “contribution” is both insignificant and simply an iteration of a known concept in the art. *See, e.g., Israel Bio-Eng’g Project v. Amgen, Inc.*, 475 F.3d 1256, 1264 (Fed. Cir. 2007). Thinking of putting a seat belt in a flying car does not make that person the joint inventor of a flying car. *See, e.g., Meng v.*

Chu, 643 Fed. App'x 990, 996 (Fed. Cir. 2016) (devising synthesis of compounds required only ordinary skill and thus not sufficient to establish joint inventorship). Indeed, the '956 Patent specification describes this known concept, stating “[m]itotic inactivation (through irradiation or mitomycin C treatment) is routinely used in mixed leukocyte reaction (MLR) assays and does not appear to greatly affect MSC cytokine secretion or immunomodulatory activities in these assays (Bocelli-Tyndall et al 2007²).” ('956 Patent at 77:39-44, AIRM00290492.) Because the idea to mitotically inactivate MSCs derived from any source was a known concept in the art, it cannot be sufficient to confer a share of inventorship by Drs. Xu and Wang over the claims of the '321 Patent.

3. Defendants' Counterclaims Do Not Promote Judicial Economy

Even if Defendants filed a new suit seeking to correct inventorship of the '321 Patent, collateral estoppel would bar such claims. The “principle of collateral estoppel, or issue preclusion, . . . bars relitigation of any factual or legal issue that was *actually* decided in previous litigation between the parties, whether on the same or a different claim.” *Keystone Shipping Co. v. New England Power Co.*, 109 F.3d 46, 51 (1st Cir. 1997) (quotation omitted); *Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1342 (Fed. Cir. 2013) (regional Circuit precedent governs general applications of collateral estoppel, but Federal Circuit precedent applies to “those aspects of such a determination that involve substantive issues of patent law”). As Defendants admit, their proposed new counterclaims arise out of the same nucleus of operative facts as Defendants' current counterclaims and Astellas's claims. (D.I. 71 at 8-9.) Disputes about factual issues like the importance of creating new ways to make MSC-cells versus merely characterizing them will be resolved in the current case and will be binding on the parties in any subsequent case. It is of no

² This article also reported test results comparing properties of irradiated and non-irradiated BM-MSCs from healthy and autoimmune patients, such as their immunomodulatory activity.

moment that the Defendants’ new counterclaims focus on dependent claims of the ’321 and ’956 Patents that have not been at issue in the current case. “Importantly, it is the issues litigated, not the specific claims around which the issues were framed, that is determinative” for the application of collateral estoppel. *AbbVie, Inc. v. Kennedy Trust for Rheumatology Research*, No. 13-cv-1358(PAC), 2014 WL 3360722, at *3 (S.D.N.Y. July 9, 2014) (quotation omitted).

C. Defendants’ Proposed Counterclaims Prejudice Plaintiffs

Defendants tacitly admit that Astellas will be prejudiced, at least to some degree, by the timing of Defendants’ amendment. (*See* D.I. 71 at 8 (“The timing of the amendment will not *seriously* prejudice Plaintiffs.”) (emphasis added).) But contrary to Defendants’ assertion, the prejudice will indeed be serious. Although Defendants assert that “[a]t most, the only additional discovery needed would be a short deposition of Dr. Wang,” Astellas does not agree. First, it is unclear why a short deposition of Dr. Wang would be sufficient when Defendants are—for the first time in this litigation—proposing to add Dr. Xu as an inventor to two patents. Clearly Dr. Xu is a central figure to these amendments, and Astellas likely would need to depose him on these new issues. Defendants imply that Astellas had an opportunity to depose Dr. Xu about their proposed counterclaims by asserting that Defendants informed Astellas of their plan to seek leave to add a new counterclaim and that they “told [Astellas] the factual basis for such a claim” “[p]rior to Dr. Xu’s deposition.” (D.I. 71 at 9 n.14.) But such an implication is wrong, as Defendants omit just how “prior” that notice was—it was provided verbally to Astellas the day before Dr. Xu’s deposition during Astellas’s deposition of ImStem CEO Mr. Men, leaving Astellas no time to prepare questions for Dr. Xu on these topics. In any event, fact discovery is closed, and Defendants’ eleventh-hour, untimely, and frivolous attempt to add new claims is not a legitimate excuse to crack it back open. It makes a mockery of the Court’s rules and scheduling orders.

In addition, obtaining a second deposition of Dr. Xu is likely to require significant time and effort, based on Defendants' previous conduct in scheduling Dr. Xu's first deposition. Dr. Xu currently lives in Macau, a fact Defendants hid behind when stalling on Astellas' repeated requests that Defendants provide a date for his deposition. In fact, Astellas first noticed Dr. Xu's deposition on February 6, 2019 and sent repeated emails since then seeking to obtain a deposition date. (*See, e.g.*, Ex. 13 (Astellas requesting deposition dates three times between February 20 and March 14, 2019, while also offering an April 9, 2019 date for Dr. Kimbrel's deposition, even though Defendants had not yet noticed it).) In the end, there was about a five-month delay from when Astellas noticed Dr. Xu's deposition (February 6, 2019) to the first date that Defendants offered (June 28, 2019) and the actual date on which the deposition occurred (July 2, 2019). (*See* Ex. 14.) Allowing this counterclaim would require additional deposition time of Dr. Xu given that he had *never* claimed he was a joint inventor of the '321 or '956 Patents,³ and given his location and Defendants' prior dilatory conduct in scheduling Dr. Xu's first deposition, an additional deposition will greatly delay this case. *EMC Corp. v. Pure Storage, Inc.*, 310 F.R.D. 194, 202 (D. Mass. 2015) (finding undue prejudice to Plaintiffs for amendment to counterclaims where it would "require revisions to the existing pretrial deadlines, increase the costs of discovery, and cause substantial delays in resolving the present dispute"). [REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

³ Complicating matters further, it is still unclear whether Defendant Xu himself is joining in Defendants' ImStem's and Wang's amended counterclaims. Although Defendants' counsel signed the motion for leave to amend on behalf of all three Defendants (D.I. 71 at 12), their proposed Amended Answer and Counterclaims is signed on behalf of only Defendants ImStem and Wang (D.I. 71-1 at 23; D.I. 71-2 at 24). Moreover, Defendants ImStem and Wang originally filed a separate Answer and Counterclaims (D.I. 20) from Defendant Xu's Answer (D.I. 33), and Defendants' counsel has not moved for leave to amend Defendant Xu's original Answer.

Separately, Astellas had no reason to inquire into any aspects of the counterclaims Defendants now assert, and therefore at the very least Astellas likely would need to serve additional interrogatories and document requests to determine Defendants' alleged facts and bases for inventorship of the new claim elements. Further, Defendants' past delays in responding to discovery requests suggests that their responses to any new discovery requests would involve significant delay. In fact, Defendants did not serve *any* of their responses to Astellas's discovery requests by their original due dates and completely failed to request an extension to Astellas's Second Set of Interrogatories until nearly *two weeks after the original due date*, despite Astellas's repeated inquiries. (*See, e.g.*, Ex. 15 (Responses due June 28, 2019, and Astellas following-up on June 29, July 2, July 10, and July 15, 2019).) Defendants' document production fared no better. Although Defendants represented on a January 24, 2019 meet and confer that their initial document production would be "substantially complete," it was not—at the very least because it did not contain any documents where Defendant Xu was the custodian. (*See* Ex. 16.) And Defendants' counsel repeatedly failed to respond to Astellas's emails and calls requesting for a meet and confer to resolve this issue. (*See id.*) Each of Defendants' counsel's repeated delays has required Astellas to expend unnecessary additional efforts to obtain the requested discovery. Introducing the need for even more discovery—and the likely additional delays and unresponsiveness from Defendants' counsel—will prejudice Astellas by diverting its resources from continuing to prepare for expert discovery and trial on the current issues in the case.

Defendants' undue delay in raising these claims until such a late stage in the litigation after the close of fact discovery prejudices Astellas, who has diligently pursued and worked toward resolution of the parties' dispute. *See Euro-Pro Operating LLC v. Dyson Inc.*, 164 F. Supp. 3d 235, 240 (D. Mass. 2016) ("allowing an amendment at this stage of proceedings [after the close of

fact discovery] would be unduly prejudicial, as it would require the reopening of fact discovery . . . in support of a legal theory that [the party] did not attempt to advance until far too late in the life of this case”).

D. Defendants’ Surreptitious Attempt to Add a New Affirmative Defense Should Be Denied

1. Defendants Make No Attempt to Argue There is Good Cause to Add Their New Affirmative Defense

Defendants offered no explanation for—or even any reference to—their inclusion of a new Statute of Limitations affirmative defense in their motion or accompanying memorandum. Thus, Defendants have waived any argument regarding this new affirmative defense, and the amendment should be denied. *Nikitine v. Wilmington Tr. Co.*, 715 F.3d 388, 390 (1st Cir. 2013) (denying motion to amend where the party “offer[ed] absolutely no explanation”); *DiVenuti v. Reardon*, 37 Mass. App. Ct. 73, 77 (1994) (denying motion to amend answer to add new affirmative defenses). As the First Circuit explained, “[f]ew principles are more sacrosanct in this circuit than the principle that ‘issues averted to in a perfunctory manner, unaccompanied by some effort at developed argumentation, are deemed waived.’” *Redondo-Borges v. United States Dep’t of Housing & Urban Dev.*, 421 F.3d 1, 6 (1st Cir. 2005) (citation omitted). Defendants had “an obligation to spell out [their] arguments squarely and distinctly, or else forever hold [their] peace.” *Id.* They did not meet their obligation. As such, Defendants necessarily fail to establish good cause to add this late defense. Notably, Defendants seek to file a reply in support of their motion. While normally Plaintiffs would not oppose such a motion, they do so here because of the Court’s interest in expeditious resolution of the motion. In any event, Defendants cannot overcome the waiver in their opening brief by raising new arguments in a reply.

2. Defendants' New Affirmative Defense is Futile and Unduly Prejudicial

Moreover, Defendants' new affirmative defense is futile because it is barred by Federal Rule of Civil Procedure 8(c), which provides that "affirmative defenses—including those based on a statute of limitations—must be raised in the defendant's answer to the plaintiff's complaint." *In re Cumberland Farms, Inc.*, 284 F.3d 216, 225 (1st Cir. 2002). "[F]ailure to plead the statute of limitations promptly 'ordinarily results in the waiver of the defense.'" *Id.* (quoting *Depositors Trust Co. v. Slobusky*, 692 F.2d 205, 208 (1st Cir. 1982)); accord *Knapp Shoes, Inc. v. Sylvania Shoe Mfg. Corp.*, 15 F.3d 1222, 1226 (1st Cir. 1994); *Jakobsen v. Mass. Port Auth.*, 520 F.2d 810, 813 (1st Cir. 1975). Defendants failed to raise this defense in their answer filed over a year and a half ago, and thus have waived it.

Additionally, Defendants' failure to raise this defense in the first instance prejudiced Astellas to gather discovery on this defense and consider the impact of such a defense. *See, e.g., Perlmutter v. Shatzer*, 102 F.R.D. 245, 249 (D. Mass. 1984) ("It seems to require little argument that where the party seeking to amend wishes to raise a defense of limitations long after the answer was first filed, a court would be remiss if it did not carefully balance the effects of such action, for it is manifest that *the risk of substantial prejudice increases in proportion to the length of defendant's delay* in seeking the amendment In sum, *the party wishing to raise the defense is obliged to plead the statute of limitations at the earliest possible moment*") (emphasis in original). Such prejudice and delay warrants denying Defendants' attempt to sneak this defense into their amended pleading.

IV. CONCLUSION

Because they would be futile, are unduly delayed, made in bad faith with dilatory motives, and prejudice Astellas, Defendants' motion to add two counterclaims, and its clandestine attempt to add a new affirmative defense, should be denied.

Dated: July 30, 2019

Respectfully submitted,

/s/ Charles H. Sanders
Charles H. Sanders (BBO# 646740)
LATHAM & WATKINS LLP
John Hancock Tower, 27th Floor
200 Clarendon Street
Boston, MA 02116
Telephone: (617) 948-6022
Facsimile: (617) 948-6001
charles.sanders@lw.com

Michael A. Morin (pro hac vice)
David P. Frazier (pro hac vice)
Rebecca L. Rabenstein (pro hac vice)
LATHAM & WATKINS LLP
555 Eleventh Street, NW, Suite 1000
Washington, DC 20004
Telephone: (202) 637-2200
Facsimile: (202) 637-2201
michael.morin@lw.com
david.frazier@lw.com
rebecca.rabenstein@lw.com

Lauren K. Sharkey (pro hac vice)
LATHAM & WATKINS LLP
330 North Wabash Avenue, Suite 2800
Chicago, IL 60611
Telephone: (312) 876-7700
Facsimile: (312) 993-9767
lauren.sharkey@lw.com

Attorneys for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that this document, which was filed with the Court through the CM/ECF system, will be sent electronically to all registered participants as identified on the Notice of Electronic Filing, and paper copies will be sent via first class mail on July 30, 2019 to those identified as non-registered participants.

/s/ Charles H. Sanders

Charles H. Sanders